Original Article

Cardio-Renal Protective Role of Cerium Oxide Nanoparticle in Preventing Histopathological Lesions, and Collagen Deposition Produced From Lead Acetate Injection in *Vivo*: Light Microscopic Examination

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ABSTRACT

Introduction: Lead, worldly is the most environmental pollutants that caused many health problems and affect all biological systems through exposure to air, water, and food sources.

Aim of the Work: The aimed of our study is to evaluate protective effect of cerium oxide nanoparticle against toxicity of lead acetate in mice cardio-renal tissues using histopathological study.

Materials and Methods: Forty male Swiss albino mice were divided into 4 groups as follows (1) control group, oral received distilled water (1ml/kg.bw); (2) lead treated group, animal injected interpertoneal by lead acetate at dose (150 mg /kg b.w, once); (3) cerium treated group: animals were given orally with cerium oxide nanoparticles at dose (0.5 mg/ kg, a and (4) cerium-lead treated group: animals given orally cerium oxide nanoparticles (0.5 mg/ kg bw) one hour prior injection of lead acetate(150 mg /kg bw). Renal and cardiac tissues were removed for histopathological and collagen deposition examinations.

Results: Histopathological examinations revealed that treatment with lead acetate induced loss of architecture in both cardiac and renal tissues as evidenced by marked degenerative change in cardomyocyte, and glomeruli as well as congested dilated blood vessels, hemorrhage and lymphocytic cells aggregation compared to control group. While, pretreatment with cerium oxide nanoparticle prior lead acetate injection resulted in inhibition the histopathological lesions and injury in cardio-renal tissues induced by lead acetate treatment. In addition to, it also prevented collagen deposition observed in lead group compared to control group.

Conclusion: In conclusions, the administration of cerium oxide nanoparticle could suppress the cytotoxicity of lead acetate and could combat tissue injury in cardio-renal tissues caused by lead acetate toxicity.

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Key Words: Cerium oxide nanoparticle; histopathological studies; lead acetate; mice; renal-cardiac tissues.

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INTRODUCTION

In the world, human and animals are exposed daily to environmental contaminants as lead. These contaminants could effect on health, behavior, and survival[1]. Lead results from the burning vehicle fuel, settles into the soil, and is absorbed by the plant, so food can be the source of lead exposure. Lead can also be found in ancient pipes, yellow tap, and cohere pipes that will pollute water. Some researchers believe that lead in the water and pipeline systems results in lead poisoning[2,3]. Lead poisoning is a well-known public health risk especially in developing countries[4]. Lead acetate exposure doses of 500 mg/kg BW caused oxidative stress and changed the expressions of apoptosis related proteins in rat liver[5].

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Recently, researchers found that high levels of lead exposure can cause brain, liver, nerve, and stomach damage, as well as permanent intellectual and developmental disabilities[6-9]. Likewise, Lead is neurotoxic, hemato and cardiovascular toxic, nephrotoxic, immunologic[7,10-13]. There is no known safe blood lead concentration. Even blood lead concentration as low as 5 mg /dL, once thought to be a safe level, may result in decreased intelligence in children, behavioral difficulties and learning problems[12].

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Uses of nanoparticles spread from engineering to medicine and from electronic devices to drug delivery systems in the last ten years[14]. Cerium oxide nanoparticles is considered as one of rare oxide earth material and have extreme surface area to ratio of volume that lead to form surface oxygen vacancies. The catalytic activity of cerium, (III) and (IV) come from their redox couple that produced from its stable and oxide form. Therefore, cerium oxide nanoparticles widely used in most industrial fields, as makeups, fuel cells, lighting science, and catalysis science technology[15,16]. Recent studies, reported that nanoceria has neuroprotective effects and mitigate ischemic brain injury after a stroke in mouse[17]. Others many researchers reported that cerium oxide nanoparticles had anti-inflammatory properties, radiation-protective effects and neuroprotective effects[18-21].

Oxidative damage induced by lead considered as one of the main mechanisms of pathologies -related lead. It is caused by disrupted prooxidant/antioxidant balance[22]. Therefore, main aim of the paper is to study the possible protective effects of cerium oxide nanoparticles on the structural lesions and fibrosis induced by lead acetate on cardiac and renal tissues of male Swiss albino mice using histopathological examinatons.

MATERIALS AND METHODS

Male Swiss albino mice (25–30 g) were used after 1 week for proper acclimatization to the animal house conditions (12- hour lighting cycle and 25 ± 2° C temperatures) with free access to standard rodent chow and water. The animals were obtained from animal house of Egyptian Drug Authority Operations and Control Sector, Cairo, Egypt. All experimental procedures were approved by the Ethical Committee on Animal Experimentation of the NODCAR, Egypt.

Ethics approval and consent to participate

Animals for experimental were accommodated and classified as well as all procedures of experimental were conducted according to guidelines of committee of the institutional animal ethics for NODCAR and were approved by the Institutional Animal Care and Use Committee (IACUC) at NODCAR (NODCAR/III/13/2021).

Chemicals

Lead acetate and Cerium oxide nanoparticles were purchased from Sigma-Aldrich (USA). Cerium oxide nanoparticles was obtained inform Nano from sigma Aldrich-USA and, its particle size was Nano powder, <25 nm and was freshly prepared before uses to prepared used dose (0.5 mg/ kg, orally, antioxidant treatment dose) according to Hirst *et al*.,[21] while Lead acetate was freshly prepared before uses to prepared used dose (150 mg /kg b.w) according to Andjelkovic *et al*.[23]. Others reagents were obtained from Sigma-Aldrich (USA).

Experimental design

Forty mice were classified into four groups at random, each group content ten mice: (1) control treated group: animals were administrated orally with distilled water (1ml D.W. / once); (2) Lead acetate treated group: animals received a single treatment of aqueous solution of lead acetate at dose (150 mg /kg b.w) according to Andjelkovic *et al*.[23] ; 3) Cerium oxide-treated group: mice in this group orally administrated with Cerium oxide nanoparticles dose (0.5 mg/ kg, orally, antioxidant treatment dose) according to Hirst *et al*.,[21] and (4) Cerium oxide-Lead acetate treated group: animals given orally Cerium oxide nanoparticles (0.5 mg/ kg bw) one hour prior oral administration of lead acetate(150 mg /kg bw). All mice were euthanized 24 h after lead acetate administration with injection of sodium pent0barbital (50 mg /k.gram body w.) then decapitation. Heart and kidney tissues for all groups were taken for histopathological investigation.

Histopathological examination

Cardiac and renal tissue were kept in 10% formaldehyde fixative (10%) for two day, washing by distilled water, and dehydration by ascending grades of alcohol. Then tissues were cleared by xylene and were inserted in paraffin wax. Sections of paraffin with thick 5 micron were Five micron thick paraffin sections were made, putt on spotless slides, to finally staine with Ehrlich's haematoxylin and Eosin for histopathological examination. Also, .2 µm-thick paraffin sections were cut into slices from these paraffin-embedded tissue blocks, deparaffinized by immersing in xylene, rehydrated and stained with Masson's trichrome staining for detection fibrosis[24]. Then both staining slide are tested under an Olympus microscope for investigation histopathological and collagen deposion.

RESULTS

Hematoxylin and eosin examination of cardiac tissues

Histological examination of cardiac sections from untreated animals revealed normal longitudinal cardiac muscular layers with vesicular nucleus (Figure 1A). In contrast to this, cardiac tissues of animals injection with lead acetate only revealed loss normal architecture, as evidence by cardiomyocytes with homogenous cytoplasm and pyknotic nucleus, hemorrhage, congested dilated blood vessels and perivascular lymphocytic cell aggregation were seen in most areas (Figure 1B). In another areas, most cardiomyocytes display degeneration fragmentation with pyknotic nuclei widely separation, while other showed atrophied cardiac muscular layers. Necrosis area with lymphocytic cell aggregation were also seen (Figure 2B). No histological changes absorbed in cardiac sections from animals treated only with Cerium Oxide nanoparticles (Figure 1C). Pretreatment with Cerium Oxide nanoparticles before lead acetate restored the normal appearance of striated cardiac muscular layers with vesicular nucleus (Figure 1D) Compared to lead treated group.

Hematoxylin and eosin examination of renal tissues

Light microscopically examination of renal sections of normal animals exhibited normal appearance of

glomeruli surrounded by Bowman's capsule and renal tubules. Epithelial cells of renal tubules show acidophilic cytoplasm and vesicular nuclei (Figure 2A). Renal section from Swiss albino mice treated with lead acetate only showed distorted normal histological architectures as evidenced by marked degenerative changes of most glomeruli, scattered marked interstitial hemorrhage in most areas compared to control group (Figure2 B1). In addition to, most renal tubules had hyaline casts in their lumens and others tubules showed severs vacuolar degenerative changes in their cytoplasm .Congested dilated blood vessels and diffused marked aggregations of inflammatory cells were also seen (Figure 2B2). On another hand, treatment with cerium oxide nanoparticles only showed no histological alterations in glomeruli tuft and renal tubules (Figure 2C) compared to control group. Similar observations were seen in renal sections of animals pretreated with cerium oxide nanoparticles prior lead acetate injection. Restoration normal histological structure of glomeruli, and renal tissues were seen when compared to lead treated group (Figure 2D).

Masson's trichroma examination of Cardiac tissues

Cardiac sections stained with Masson's stain to estimat collagen deposition. Massion's trichrome stain revealed that small amount of collagen fiber deposition could be recorded in normal cardiac sections (Figure 3A) and animals treated only with cerium oxide nanoparticles (Figure 3C). While treatment with lead acetate resulted in accumulation of collagen deposition (Figure 3B) compared to control group (Figure 3A). Pretreatment with cerium Oxide nanoparticles before lead acetate could be inhibited collagen deposition induced by lead (Figure 3D) compared with lead treated group.

Masson's trichroma examination of renal tissues

Massion's trichrome staining revealed no collagen fiber deposition observed in section of renal tissue from control animals (Figure 4A) and animals treated only with cerium oxide nanoparticles (Figure 4c). In contrast, animals treated with lead acetate only showed high collagen fiber accumulation compared to control group (Figure 4B). When pretreatment with cerium Oxide nanoparticles before lead revealed disappearance of collagen fiber (Figure 3D) compared to lead treated group (Figure 4B).

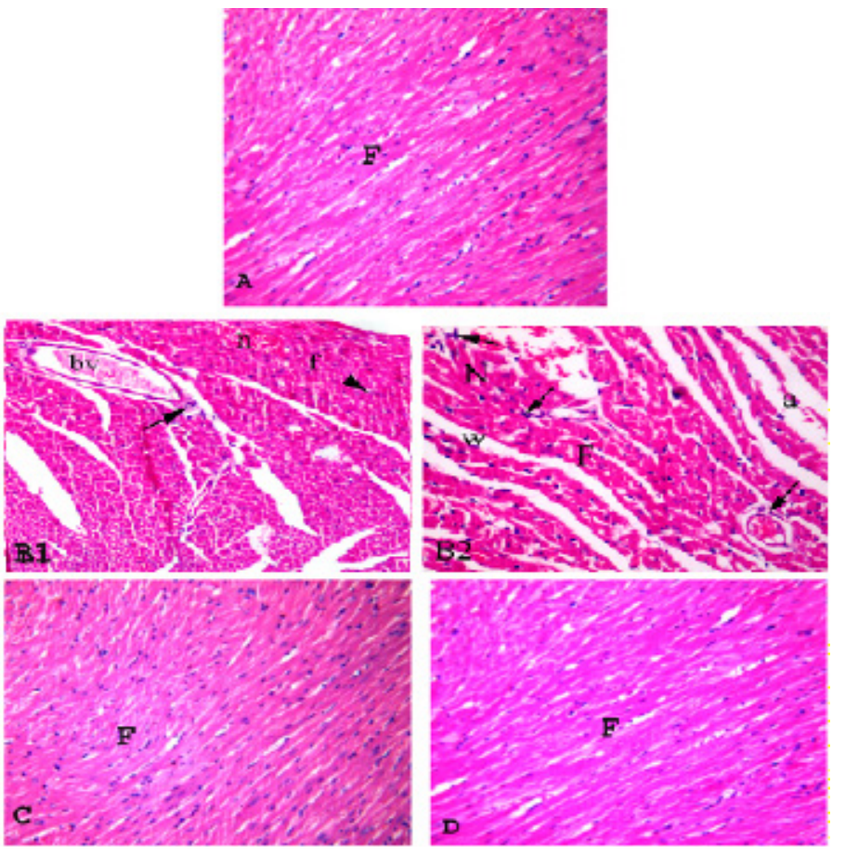

Fig. 1: Light photomicrograph of cardiac section from: (A) control mice showing normal architecture of striated cardiac muscular layers with vesicular nucleus (F). (B1) Lead treated group only showing loss of normal structure, area of cardiomyocytes showed homogenous cytoplasm (f) with pyknotic nucleus (arrow head) and congested dilated blood vessels (bv). Hemorrhage (h) and Perivascular lymphocytic cells aggregation were seen (arrow). (B2) Lead treated group only showing atrophied cardiac muscular layers (a) and large area of degenerated fragmented cardiac muscles (F) widely separation (w). In addition to, area of necrosis of (N) and lymphocytic cells aggregation (arrow) were also seen. (C) Cerium treated group showing normal appearance of longitudinal cardiac muscular layers and nucleus (F), and (D) Cerium Lead treated group showing striation of cardiac muscular layers with vesicular nucleus (F). (H&E, x200)

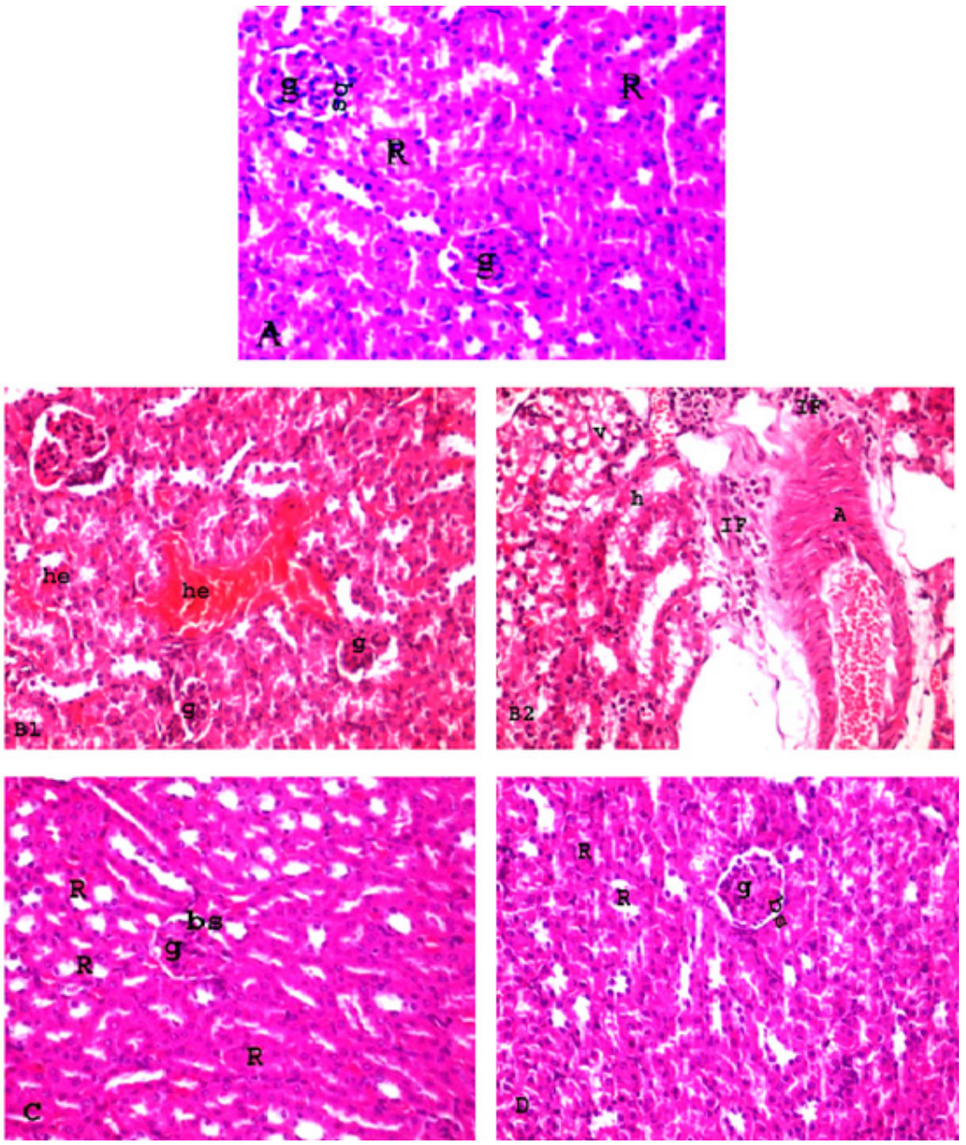

Fig. 2: Light photomicrograph of renal section from: (A) control mice normal mice showing normal architecture with normal appearance of glomeruli (g) surrounded by Bowman's space (bs) as well as renal tubules (R), (B1) Lead treated group only showing distorted normal histological architectures: marked scattered interstitial hemorrhage (he), most glomeruli with severe degenerative changes (g), (B2) Lead treated group only showing most renal tubules with hyaline casts in their lumens (h) and severs cytoplasmic vacuolar degenerative changes (V) in others tubules. Marked congested dilated blood vessels (A) and diffused marked aggregations of inflammatory cells (IF) were also seen., (C) Cerium treated group showing normal histological structure of the glomeruli surrounded by Bowman's space (bs) as well as renal tubules , and (D) Cerium Lead treated group showing normal appearance of glomeruli (g), Bowman's space (bs) and renal tubules (R). (H&E, x200).

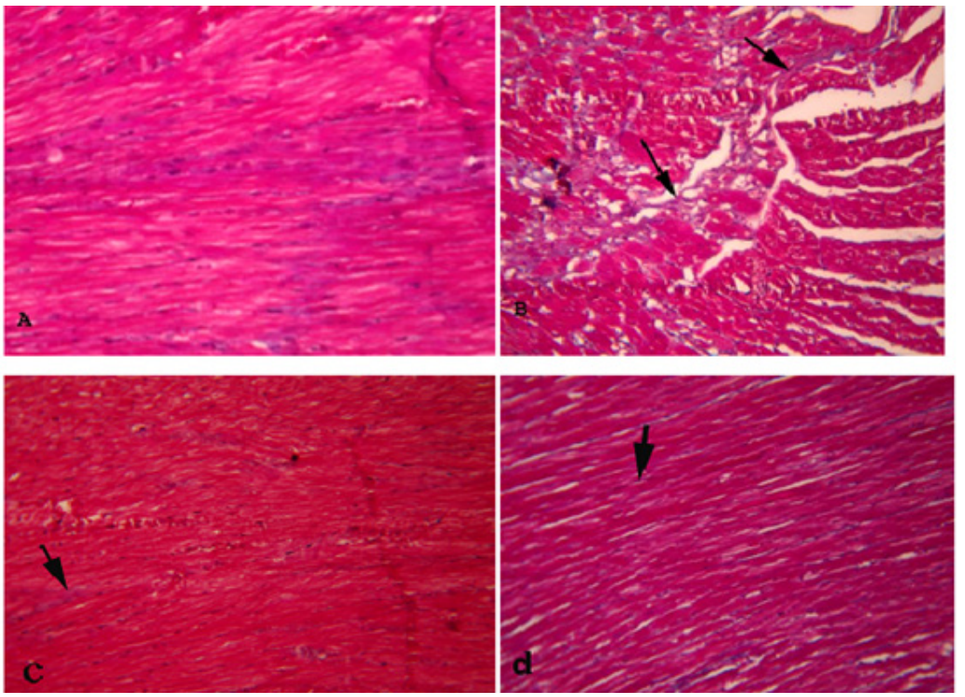

Fig. 3: Light photomicrograph of cardiac section from: (A) control mice normal mice showing minimal collagen fibers deposition (arrow), (B) Lead treated group only showing high amount of collagen fibers deposition (arrow)., (C) Cerium treated group showing minimal collagen fibers deposition (arrow), and (D) Cerium Lead treated group showing low amount of collagen fibers deposition (arrow). Normal cells are stained pink color while collagen fiber accumulation determined heart fibrosis (Arrow) and stained blue color (Massion's trichrome stain, x200).

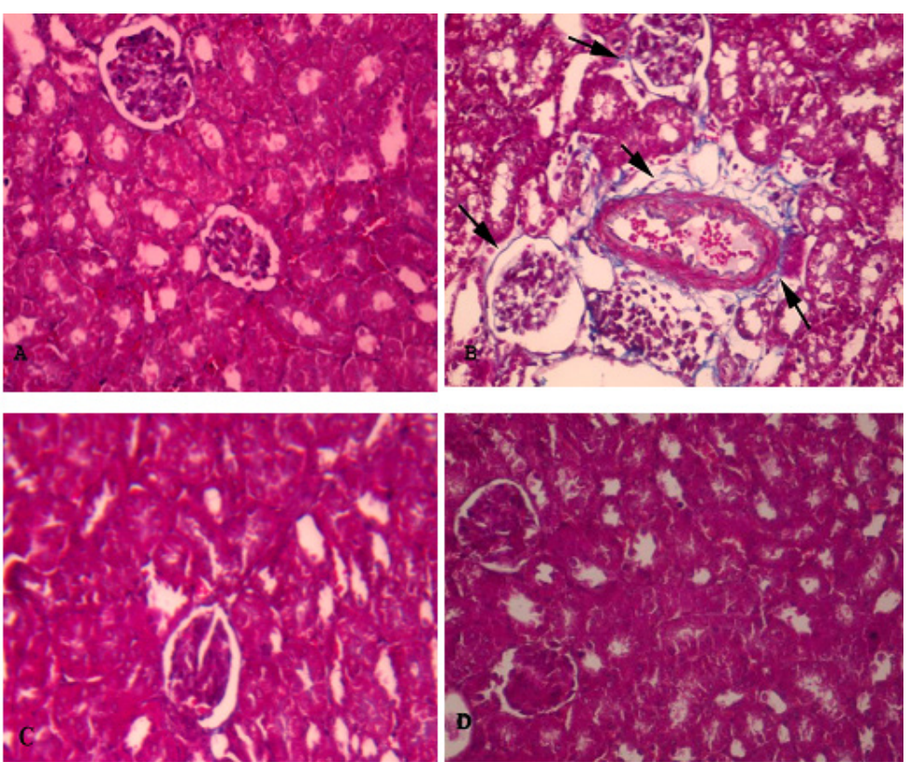

Fig. 4: Light photomicrograph of renal section from: (A) control mice normal mice showing no collagen fibers deposition., (B) Lead treated group only showing high amount of collagen fibers deposition (arrow) (C) Cerium treated group showing no collagen fibers deposition, and (D) Cerium Lead treated group showing disappearance collagen fibers deposition. Normal cells are stained pink color while collagen fiber accumulation determined heart fibrosis (Arrow) and stained blue color (Massion's trichrome stain , x200).

DISCUSSION

Lead, as noxious heavy metal for public health. Many chronic diseases could be caused by exposure to low-level from lead exposure as infertility, diabetes, renal disease, and cancer etc.)[25]. Therefore, in the current study the possible protective role of cerium oxide nanoparticles (0.5 mg/ kg bw, orally) against toxicity acetate and fibrotic action of lead on cardiac and renal tissues of Swiss albino mice were evaluated, using histopatholological studies. Our result reported that administration of lead acetate at dose 150mg / kg bw, resulted in histopathological alterations, and accumulation of collagen fiber in cardiac and renal tissues, these were in agreement with[7,23].

In our study, the observed histopathological alterations induced by lead acetate administration in tested tissues could be attributed to its accumulation the tissues[23]. Lead was undergoing intestinal absorption after its oral administration. It is transported via blood and is distributed by red blood cells and plasma proteins, mainly albumin in different tissues[26]. Inflammatory cells aggregation, in the present study, could be attributed to elevation the pro-inflammatory cytokine, IL-6 by Lead acetate administration[7] and theses aggregation of inflammatory cells could be considered as one of reason of collagen deposition observed in tested tissues[27].

Collagen deposits noticed in cardiac-renal tissues of mice treated with lead acetate, in present study could be explained by elevation of reactive oxygen species[23,28] that lead to activated fibrogenic gene expression and transforming growth factor-β (TGF-β)[29,30]. The pleiotropic transforming growth factor-β (TGF-β) family forming of TGF-β1, −β2, and −β3, has diverse roles in the body, and its exciting effects on fibrosis (especially TGF-β1) are well recorded[31,32] in cardiac[33] and renal tissues[34].

Reason for observed heart toxicity of lead acetate in the present study, is increasing of triglycerides, LDL, and total cholesterol, these factor involved in the development of heart disease while another reason for kidney toxicity of Lead acetate administration is increasing of urea and creatinine level[7]. Creatinine, Urea, and uric acid are indicators for renal function in routine analysis. Impairment of the glomrerular function and tubular damage of the kidneys is causing of increase urea and creatinine levels in the serum[35]. Other mechanisms that explained cardiac and renal damage induced by lead acetate in the present study are elevation of oxidative stress markers, lipid peroxidation and declination of antioxidant enzymes[7,23,36-38].

Oxidative stress consider as major mechanism of lead toxicity[4]. Exposure to lead could be caused excessive reactive oxygen species generation and depletion of antioxidant reserves[39,40]. Also, Lead could be exchange zinc ions that consider as essential cofactors for antioxidant enzymes[39].

Moreover, ours study also reported that pretreatment with cerium oxide nanoparticles prior lead acetate administration prevented histopathological alterations and collagen deposition in cardiac-renal tissues induced by lead acetate, these were supported by Linse *et al*.,[41]. In our study, observed inhibition activity for cerium oxide nanoparticles versus lead acetate toxicity in cardiac-renal tissues could be attributed to antioxidant activity and anti-inflammatory properties[42]. It also, has ability to reduce oxidative stress, and scavenge of free radicals[17,18,20,43-45]. The mechanism of action to cerium oxide nanoparticles referred to its ability to reversibly switch between the 3+ and 4+ oxidation states as well as its regenerative antioxidant properties could be attributed to the valence structure of the cerium atom combined with inherent defects in the crystal lattice and oxygen defect structure[46,47].

Antioxidant properties of cerium oxide nanoparticles have been established using a superoxide dismutase mimetic activity-based model[19]. Previous studies reported that cerium oxide nanoparticles have a potential antioxidant property that attributed to high biocompatibility and its possibility to regenerate the initial oxidation state through redox cycling reactions[48].

Likewise, Cerium oxide nanoparticles have the ability to prevent retinal degeneration induced by intracellular peroxide molecules[49]. Similar, Zhang *et al*.[50], reported that in a dose-dependent manner, cerium oxide nanoparticles could inhibit apoptosis induced by hydrogen peroxide (H_2O_2)-in mouse bone marrow stromal cells of mice through its antioxidants properties and its ability to limit the amount of reactive oxygen species to prevent or treat osteoporosis. These also supported by work done by Hamzeh *et al*[51] who reported protective role of cerium oxide nanoparticle against testicular damage produced by cyclophosphamide via anti-oxidative and anti-apoptotic activity. It down- regulates caspase-3 and reduces reactive oxygen species, and lipid peroxidation. Further, Pagliari,[52] and Saleh,[53] reported that nanoceria has an effective antioxidant, high potential of nanoceria for controlling ROS-induced cell damage, a s well as able to protect cardiac progenitor cells from H_2O_2-induced cytotoxicity.

CONCLUSIONS

Our research indicated that a cerium oxide nanoparticle has ability to prevent most of the histopathological lesions in the cardiac and renal tissues induced by lead toxicity as manifested by the light microscopic examination. Cerium oxide nanoparticles also prevent collagen fiber deposition in cardiac and renal tissues.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCES

1. Abdelhamid, F. M. ; Mahgoub H. A. ; Ateya, A.I. Ameliorative effect of curcumin against lead acetate–induced hemat0-biochemical alterations, hepatotoxicity, and testicular oxidative damage in rats . Environmental Science and Pollution Research (2020) 27, 10950–10965. https://doi.org/10.1007/s11356-020-07718-3
2. Khan, M. S. H. ; Mostofa, M.; Jahan, M. S. *et al*. Effect of garlic and vitamin B-c0mplex in lead acetate induced toxicities in mice. Bangladesh Journal of Veterinary Medicine, 2008, 6 (2), 203–210. https://doi.org/10.3329/bjvm.v6i2.2337
3. El-khadragy , M.; Al-Megrin, W A. ; AlSadhan, N A. ; Metwally , D. M. ; El-Hennamy, R. E. ; Salem, F. E. H.; Kassab , Rami B. ; and Abdel Moneim, A. E. Impact of C0enzyme Q10 Administration on Lead Acetate-Induced Testicular Damage in Rats. Hindawi Oxidative Medicine and Cellular Longevity 2020, 1-12. https://doi.org/10.1155/2020/4981386
4. Kumar, S. R.; and Devi, A. S. Lead toxicity on male reproductive system and its mechanism: a review," Research Journal of Pharmacy and Technology 2018, 11(3), 1228, 2018. https://doi.org/ 10.5958/0974-360X.2018.00228.7
5. El-Boshy, M .E.; Refaat, B.; Qasem, A.H.; Khan, A.; Ghaith, M.; Almasmoum, H.; Mahbub, A.; Almaimani, R.A. The remedial effect 0f thymus vulgaris extract against lead toxicity-induced oxidative stress, hepatorenal damage, immunosuppression, and hematological disorders in rats. Environ Sci Pollut Res Int 2019,26, 22736–22746. https://doi.org/10.1007/s11356-019-05562-8
6. Musa, S. A.; Omoniye, I.M.; Hamman, W. O.; Ibegbu, A. O.; Umana, U. E . Preventive activity of ascorbic acid 0n lead acetate induced cerebellar damaged in adult Wistar rats. Medical and Health Science Journal 2012, 13, 99-104. https://doi.org/574:543.9+613.632:612.015
7. Offor, S. J.; Mbagwu, H. O. C. ; Orisakwe, O. E. Lead Induced Hepat0-renal Damage in Male Albino Rats and Effects of Activated Charcoal. Frontiers in Pharmacology 2017, 8 (107), 1-10. https://doi.org/10.3389/fphar.2017.00107
8. Saleh1, S, M. ; Meligy, F. Y. Study on toxic effects of lead acetate on cerebellar c0rtical tissue of adult albino rats and the role of vitamin E as a protective agent. Ain Shams Journal of Forensic Medicine and Clinical Toxicology 2018, 31,110-118. https://doi.org/10.21608/AJFM.2018.15884
9. Bauchi, Z.M.; Kizito, D.; Alhassan, A.W.; Akpulu, S.P.; Timbuak ,J.A. Effect of Aqueous Seed Extract of Nigella Sativa on Lead-Induced Cerebral Cortex Toxicity in Long Evans Rats. Bayero Journal of Pure and Applied Sciences 2016, 9(1), 48 – 52. https://doi.org/10.4314/bajopas.v9i1.8
10. Chen, J.; Chen, Y.; Liu, W.; Bai, C.; Liu, X.; Liu, K.; Li, R.; Zhu , J.-H. ; Huang C. Developmental lead acetate exposure induces embryonic toxicity and memory deficit in adult zebra fish. Neurotoxicology and Teratology 2012, 34, 581–586. https://doi.org/ 10.1016/j.ntt.2012.09.001
11. Ibrahim, N. M.; Eweis, E. A.; El-Beltagi, H.S .; Abdel-Mobdy, Y.E. Effect of lead acetate toxicity on experimental male albino rat. Asian Pac J Trop Biomed. 2012, 2(1), 41–46. https://doi.org/10.1016/S2221-1691(11)60187-1
12. Kalia, K.; and Flora, S. J. Strategies for safe and effective therapeutic measures for chr0nic arsenic and lead poisoning. J. Occup. Health 2005, 47, 1–21. DOI: https://doi.org/ 10.1539/joh.47.1
13. Wani, A. L.; Ara, A.; Usmani, J. A. Lead toxicity: a review. Interdiscip Toxicol. 2015, 8(2), 55–64. https://doi.org/ 10.1515/intox-2015-0009
14. Shah, S. S.; Denham, L. V.; Jasmine, R. E.; *et al*. Drug delivery to the posterior segment of the eye for pharmacologic therapy. Expert Review of Ophthalmology. 2010, 5 (1), 75–93. https://doi.org/ 10.1586/eop.09.70
15. Corma, A.; Atienzar, P.; Garcı´a, H.; Chane-Ching, J.Y. Hierarchically mes0structured doped cerium oxide with potential for solar-cell use. Nat Mater 2004, 3, 394–397. https://doi.org/ 10.1038/nmat1129
16. Zhai, Y.Q.; Zhang, S.Y.; Pang, H. Preparation, characterization and photo catalytic activity of cerium oxide nanocrystalline using ammonium bicarbonate as precipitan. Mater Lett. 2007, 61, 1863–1866. https://doi.org/ 10.1016/j.matLet.2006.07.146
17. Estevez, A.Y.;, Pritchard, S. ; Harper, K.; Aston, J.W.; Lynch, A.; Lucky, J.J.; Ludington, J.S;. Chatani, P.; Mosenthal, W.P.; Leiter, J.C.; Andreescu, S.; Erlichman, J.S. Neur0protective mechanisms of cerium oxide nanoparticles in a mouse hippocampal brain slice model of ischemia. Free Radic Biol Med 2011, 51, 1155-1163. https://doi.org/10.1016/j.freeradbiomed.2011.06.006
18. Tarnuzzer, R.W.; Colon, J.; Patil, S.; Seal, S. Vacancy engineered ceria nanostructures for protection from radiation induced cellular damage. Nano Lett. 2005, 5, 2573–2577. https://doi.org/10.1021/nl052024f
19. Korsvik, C.; Patil, S.; Seal, S.; Self, W.T. Superoxide dismutase mimetic pr0perties exhibited by vacancy engineered ceria nanoparticles. Chem Commun. 2007, 14, 1056-1058. https://doi.org/ 10.1039/b615134e
20. Das, M.; Patil, S.; Bhargava, N.; Kang, J.F.; Riedel, L.M.; Seal, S.; Hickman, J.J. Auto-catalytic ceria nanoparticles offer neuroprotection to adult rat spinal cord neurons. Biomaterials. 2007, 28, 1918–1925. https://doi.org/10.1016/j.biomaterials.2006.11.036
21. Hirst, S. M.; Karakoti, A.; Singh, S.; Self, W.; Tyler, R.; Seal, S.; Reilly, C. M. Bio-distribution and In *Vivo* Antioxidant Effects of Cerium Oxide Nanoparticles in Mice. 2011, 107-118. https://doi.org/10.1002/tox.20704

22. Patrick, L. Lead toxicity part II: the role of free radical damage and the use of antioxidants in the pathology and treatment of lead toxicity. Altern Med Rev. 2006, 11(2), 114–127. [PubMed: 16813461]. https://doi.org/20775767

23. Andjelkovic, M.; Djordjevic, A. B.; Antonijevic, E.; Antonijevic, B.; Stanic, M.; Kotur-Stevuljevic, J.; Spasojevic-Kalimanovska, V.; Jovanovic, M.; Boricic, N.; Wallace, D.; Bulat, Z. Toxic effect of acute cadmium and lead exposure in rat blood, liver, and kidney. International Journal of Environmental Research and Public Health. 2019 , 16(2), 274. https://doi.org/10.3390/ijerph16020274

24. Bancroft, J.; Gamble, M. Theory and Practice of Histological Techniques. 6th ed.Churchill Livingstone, London. 2008, 165–175, 340–348. https://doi.org/9780443102790 0443102791

25. Orisakwe, O. E. Lead and Cadmium in Public Health in Nigeria: physicians neglect and pitfall in patient management. N. Am. J. Med. Sci. 2014, 6, 61–70. https://doi.org/ 10.4103/1947-2714.127740

26. Aladaileh, S.H.; Khafaga,A.F.; El-Hack, M.E.A.; Al-Gabri, N.A.; Abukhalil,M.H.; Alfwuaires, M.A.; Bin-Jumah, M, ;Alkahtani, S,; Abdel-Daim, M.M.; Aleya, L.; Abdelnour, S. Spirulina platensis ameliorates the sub chronic toxicities of lead in rabbits via anti-oxidative, anti-inflammatory, and immune stimulatory properties. Sci Total Environ 2020, 701,134879. https://doi.org/10.1016/j.scitotenv.2019.134879

27. BaSalamah, M.A.; Abdelghany, A.H.; El-Boshy, M.; Ahmad, J.; Idris, S.; Refaat, B. Vitamin D alleviates lead induced renal and testicular injuries by immunomodulatory and antioxidant mechanisms in rats. Sci Rep 2018, 8,4853. https://doi.org/10.1038/s41598-018-23258-w

28. Wynn, T.A. Cellular and molecular mechanisms of fibrosis. J Pathol. 2008, 214(2), 199–210. https://doi.org/10.1002/path.2277.

29. Autifi, M. A. H.; Mohamed, W.Y.; Abdul -Haye, W. M.; Elbaz, K. R. The possible protective role of vitamin c against toxicity induced by lead acetate in liver and spleen of adult albino rats (light and electron microscopic study). The Egyptian Journal of Hospital Medicine 2018, 73 (10), 7650-7658. https://doi.org/10.12816/EJHM.2018.19896

30. Bartosz, G. Reactive oxygen species: destroyers or messengers. Biochemical Pharmacology 2008, 77(8), 1303-1315. https://doi.org/10.1016/j.bcp.2008.11.009

31. Dobaczewski, M.; Chen, W.; Frangogiannis, N.G. Transforming growth factor (TGF)-beta signaling in cardiac remodeling. J Mol Cell Cardiol. 2011 Oct; 51(4): 600–606.J Mol Cell Cardiol 2011. https://doi.org/10.1016/j.yjmcc.2010.10.033

32. Kim, K.K.; Sheppard, D.; Chapman, H.A. TGF-beta1 signaling and tissue fibrosis. Cold Spring HarbPerspect Biol 2021, 1-32. [PubMed: 28432134] . https://doi.org/ 10.1101/cshperspect.a022293

33. Cowling, R. T.; Kupsky, D.; KAHN, A. M.; Daniels, L. B. and GreenberG B. H. Mechanisms of cardiac collagen deposition in experimental models and human disease. Transl Res. 2019 , 209, 138–155. https://doi.org/10.1016/j.trsl.2019.03.004.

34. Kamejima, S.; Tatsumi, N.; Anraku, A.; Suzuki, H.; Ohkido, I.; Yokoo, T.; & Okabe, M.Gcm1 is involved in cell proliferation and fibrosis during kidney regeneration after ischemia–reperfusion injury. Scientific Reports 2019, 9, 7883,1-14. | https://doi.org/10.1038/s41598-019-44161-y

35. Ahmed, N. M.; Sabra. H. A. Reno- protective effect of graviola (annona muricata) leaves against lead acetate toxicity on experimental albino rats. Biochemistry Letters 2018, 13(1), 1-13. https://doi.org/10.21608/BLJ.2018.47203

36. Pratap, M. and Indira, P. Protective effects of ginger (Zingiber officinale) extract against lead induced oxidative stress on liver antioxidant enzymes in male Albino rats. Int. J. Pharm. Bio. Sci., 2014, 5 (2), 888-894. https://doi.org/10.1159/000479789

37. Lotfi-Ghahramanloo, M.; Baghshani, H. Ameliorative Effects of Caffeic Acid on Lead Accumulation and Oxidative Stress in Lead-Exposed Mice. Zahedan J Res Med Sci. 2016 , 18(5), 1-5. e6674. https://doi.org/ 10.17795/zjrms-6674

38. Wahyuningsih , S. P. A.; Savira, N. I. I.; Anggraini, D.W.; Winarni, D.; Suhargo, L.; AdiKusuma, B.W.; Nindyasari, F.; Setianingsih, N. and Mwendolwa, A. A.. Antioxidant and nephroprotective effects of okra pods extract (abelmoschus esculentus l.) against lead acetate-induced toxicity in mice. Hindawi Scientifica 2020, 2020, 1-10. https://doi.org/10.1155/2020/4237205

39. Flora, S. J.; Flora, G.; Saxena, G.; and Mishra, M. Arsenic and lead induced free radical generation and their reversibility following chelation. Cell Mol. Biol. 2007, 53, 26–47. https://doi.org/10. 1170/T773

40. Liu, C.M.; Yang, H.X.; Ma, J.Q.; Yang, W.; Feng, Z.J.; Sun, J.M.; Cheng, C.; Li, J.; Jiang, H. Role of AMPK pathway in lead-induced endoplasmic reticulum stress in kidney and in paeonol-induced protection in mice. Food Chem Toxicol 2018, 122,87–94. https://doi.org/10.1016/j.fct.

41. Linse, S.; Cabaleiro-Lago, C.; Xue, W-F.; *et al*. Nucleation of protein fibrillation by nanoparticles. Proceedings of the National Academy of Sciences of the United States of America. 2007, 104 (21), 8691-8696. https://doi.org/10.1073/pnas.0701250104

42. Colon, J.; Herrera, L.; Smith, J.; Patil, S.; Komanski, C.; Kupelian, P.; Seal, S.; Jenkins, D.W.; Baker, C.H. Protection from radiation-induced pneumonitis using cerium oxide nanoparticles. Nanomed Nanotechnol Biol Med 2009, 5, 225–231. https://doi.org/ 10.1016/j.nano.2008.10.003

43. Schubert, D.; Dargusch, R.; Raitano, J.; Chan, S.W. Cerium and yttrium oxide nanoparticles are neuroprotective. Biochem Biophys Res Commun . 2006, 342, 86–91. https://doi.org/ 10.1016/j.bbrc.2006.01.129

44. Amin, K.A.; Hassan, M.S.; Awadel, S.T.; Hashemel, K.S . The protective effects of cerium oxide nanoparticles against hepatic oxidative damage induced by monocrotaline. Int J Nanomed. 2011, 6, 143–149. https://doi.org/10.2147/IJN.S15308

45. Amer, M.A.; Farahat, F.Y .; Abd El-Khalik, A.M.; and Hassan, H.E. Protective Effect of Cerium Oxide Nanoparticles on Oxaliplatin induced Neurotoxicity in Adult Male Albino Rats. 2020, 18(1),52-67. https://doi.org/10.21608/ZJFM.2019.7954.1023.

46. Rzigalinski, B.A . Nanoparticles and cell longevity. Technol Cancer Res Treat 2005, 4, 651–659. https://doi.org/ 10.1177/153303460500400609

47. Nolan , M.;Parker, S. C. ;Watson ,G.W. Reduction of NO2 on ceria surfaces. J Phys Chem B , 2006, 110, 2256–2262. https://doi.org/10.1021/jp055624b

48. Karakoti, A.; Singh, S.; Dowding, J.M.; Seal, S.; Self, W.T . Redox-active radical scavenging nanomaterials. Chem. Soc. Rev. 2010, 39, 4422–4432. https://doi.org/10.1039/B919677N

49. Chen, J.; Patil , S.; Seal, S.; McGinnis, J.F., Rare earth nanoparticles prevent retinal degeneration induced by intracellular peroxides. Nat Nanotechnol. . 2006, 1,142–150. https://doi.org/ 10.1038/nnano.2006.91

50. Zhang, Q.; Ge, K.; Duan, J.; Chen, S.; Zhang, R.; Zhang, C.; Wang, S.; Zhang, J. Cerium oxide nanoparticles protect primary mouse bone marrow stromal cells from apoptosis induced by oxidative stress. J Nanopart Res. 2014, 16, 2697. https://doi.org/ 10.1007/s11051-014-2697-3

51. Hamzeh, M.; Hosseinimehr, S. J.; Karimpour, A.; Mohammadi, H. R.; Khalatbary, A.R.; Amiri, F.T. Cerium oxide nanoparticles protect cyclophosphamide-induced testicular toxicity in mice. International Journal of Preventive Medicine 2019, 1-9. https://doi.org/ 10.4103/ijpvm.IJPVM_184_18

52. Pagliari, F.; Mandoli, C.; Forte, G.; Magnani, E.; Pagliari, S.; Nardone, G.; Licoccia,S.; Minieri, M.; Di Nardo, P.; and Traversa, E. Cerium Oxide Nanoparticles Protect Cardiac Progenitor Cells from Oxidative Stress. ACS Publications research 2012, 6(5), 3767–3775. https://doi.org/10.1021/nn2048069

53. Saleh, H.; Nassar , At. M. K.; Noreldin , A. E.; Samak, D.; Elshony, N.; Wasef, L.; Elewa, Yaser H.A.; Hassan, S. M. A.; Abdullah A. Saati 8, Helal F. Hetta 9, Gaber El-Saber Batiha 4,* , Masakazu Umezawa 10 , Hazem M. Shaheen 4,* and Yasser S. El-Sayed 1,* Chemo-Protective Potential of Cerium Oxide Nanoparticles against Fipronil-Induced Oxidative Stress, Apoptosis, Inflammation and Reproductive Dysfunction in Male White Albino Rats. Molecules 2020, 25, 3479. https://doi.org/10.3390/molecules25153479

الملخص العربى

الدور الوقائي في القلب والكلى لجسيمات أكسيد السيريوم النانوية لمنع التغيرات النسيجية المرضية وترسب الكولاجين الناتج من حقن خلات الرصاص في الجسم الحي: فحص ميكروسكوب ضوئي

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الخلاصة: الرصاص عالميا هو أكثر ملوثات البيئة التي تسبب العديد من المشاكل الصحية وتؤثر على جميع العمليات البيولوجية من خلال التعرض للهواء والماء ومصادر الغذاء.

هدف العمل: الهدف من دراستنا هو تقييم التأثير الوقائي لجسيمات أكسيد السيريوم النانوية ضد سمية خلات الرصاص في الأنسجة القلبية والكلوية للفئران باستخدام دراسة الهستوباثولوجية والهستوكمستري.

المواد والأساليب: تم تقسيم أربعين ذكرًا من الفئران البيضاء السويسرية إلى ٤ مجموعات على النحو التالي (١) مجموعة الطبيعية، تم تناولها عن طريق الفم الماء المقطر (١ مل / كجم وزن الجسم)؛ (٢) المجموعة المعالجة بالرصاص: الحيوانات تحقن باستيات الرصاص بجرعة (١٥٠ مجم / كجم من وزن الجسم، مرة واحدة)؛ (٣) المجموعة المعالجة بالسيريوم: أعطيت الحيوانات عن طريق الفم جزيئات أكسيد السيريوم النانوية بجرعة (٠,٥ مجم / كجم) و(٤) المجموعة المعالجة بالسيريوم والرصاص: الحيوانات فيها أُعطيت جزيئات نانوية من أكسيد السيريوم عن طريق الفم (٠,٥ ملغم / كغم من وزن الجسم) قبل ساعة واحدة من الحقن باستيات الرصاص (١٥٠ ملغم / كغم من وزن الجسم). تمت إزالة أنسجة الكلى والقلب لإجراء فحوصات الهستوباثولوجية والهستوكمستري(دراسة الكولاجين).

النتائج: كشفت الفحوصات النسجية أن العلاج باستيات الرصاص تسبب في فقدان التركيب الطبيعي في كلا من أنسجة القلب والكلوي كما يتضح من التغير التدميري الملحوظ في الخلايا العضلية القلبية، والكلوية وكذلك اتساع الأوعية الدموية والنزيف وتجمع الخلايا الليمفاوية مقارنة بالمجموعةالطبيعية. بينما المعالجة المسبقة بالسيريوم أدى حقن أكسيد النانو قبل حقن استيات الرصاص الي منع التغيرات الهستوباثولوجية. بالإضافة إلى أنه يمنع أيضًا ترسب الكولاجين الذي لوحظ في المجموعة الرصاص مقارنة بالمجموعة الطبيعية.

الإستنتاج: في الاستنتاجات، يمكن أن يؤدي إعطاء الجسيمات النانوية لأكسيد السيريوم إلى تثبيط السمية النسجية لاستيات الرصاص ويمكن أن يمنع إصابة أنسجة القلب والكلى الناجمة عن سمية خلات الرصاص.